REMARKS

Claims 1-8, 10-18, 21-28, 30-37, 40-48, 50-56, 58 and 72 presently appear in this case. No claims have been allowed. The official action of June 6, 2006, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to the inhibition of neuronal secondary degeneration, the promotion of nerve regeneration, and the protection of nerves from glutamate toxicity by the administration of poly-Glu,Tyr. It further relates to a method for down-regulation of the suppressive activity of $CD4^+CD25^+$ regulatory T cells (Treg) on $CD4^+CD25^-$ effector T cells (Teff) in an individual suffering from a neurological or neurodegenerative injury, condition, disorder or disease by the administration of poly-Glu,Tyr. Administration of poly-Glu,Tyr also provides neuroprotection to an individual suffering from a neurological injury or from a neurological or neurodegenerative disease, disorder or condition. The invention also relates to protecting nerves from the effects of a neurotoxin, such as an organophosphate nerve gas.

Election/Restrictions

The present application was filed with 71 claims. Following the Restriction Requirement of December 20, 2005, applicants elected with traverse Group I: claims 1-58, drawn to methods of administering poly-Glu,Tyr, and "stroke" as the specific disease. Claims 59-71 for an article of manufacture, Invention II, have now been cancelled. The traverse of the remainder of the restriction requirement, with respect to the diseases, was not accepted by the examiner and the restriction requirement was made final. Reconsideration of the restriction requirement with respect to the diseases is again respectfully urged.

The examiner states that claims drawn to treatment of such diverse diseases cannot share a common technical feature. However, the examiner apparently fails to note that no diseases are mentioned in claim 1. The invention, as claimed in claim 1, is not directed to the "treatment" of any disease. It is directed to the inhibition of neuronal secondary degeneration, promotion of nerve regeneration in the CNS or PNS, and protection of nerves from glutamate toxicity. Claim 2 emphasizes that persons in need of inhibition of neuronal secondary degeneration include those suffering from the neurodegenerative effects of an injury, disease, disorder or condition that has caused primary neuronal damage. Thus, it is clear that the invention is not directed to treatment of

diverse diseases, but is directed to the inhibition of secondary neuronal degeneration caused by the neurodegenerative effects of an injury, disease, disorder or condition that has caused primary neuronal damage. Regardless of the diverse nature of the injuries, diseases, etc., that may have caused the primary damage, the present invention is directed to inhibition of neurodegeneration that is secondary thereto. This is a common technical feature and the entire scope of claims 1 and 2 should be examined.

With respect to the aspect of the present invention directed to protection of nerves from glutamate toxicity, this is the common feature of the present invention when administered to patients with any of various conditions involving glutamate toxicity. Thus, for claims 10-15, the common technical feature is protection from glutamate toxicity. Many injuries, diseases and conditions are caused or exacerbated by glutamate toxicity. The present claims are not drawn to the treatment of these diseases, but only to protection from glutamate toxicity in patients who may have these diseases and are thus in need of protection from glutamate toxicity. The fact that many diseases of varying etiologies may be caused or exacerbated by glutamate toxicity is irrelevant because the claims are not directed to the treatment of such diseases. The common technical feature in

all of the treatments is the protection from glutamate toxicity and therefore the entire scope of claims 1 and 10-15 should be examined in this case. The conditions in claims 16-18 are also conditions that benefit from promotion of nerve regeneration. Thus, they too should all be examined together as the common technical feature is the fact that the patient is being protected from glutamate toxicity or will benefit from the promotion of nerve regeneration.

Claim 21 ties in all of the features of the preamble of claim 1 and explains the common technical feature of them all. In each case, the effect is achieved by the power of poly-Glu,Tyr to down-regulate the suppressive activity of Treg cells on Teff cells. Thus, these claims are directed to a common technical feature and, if these claims are examined and found to be allowable, then all of the dependent claims must be examined and found to be allowable. It should be noted that section 10.06 of Chapter 10, "Unity of Invention" in PCT/GL/ISPE/1 states:

> Unity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims.

MPEP 1893.03(d) makes explicit that these Guidelines are applicable to unity of invention practice in national stage applications.

For all of these reasons, reconsideration and withdrawal of the restriction requirement among the various injuries, diseases and conditions are respectfully urged.

Claim Objections

Claims 4, 23 and 42 were objected to because "they recite non-elected subject matter, specifically diseases other than stroke." This objection is respectfully traversed.

First of all, as discussed above, claims 1 and 2 have now been amended to emphasize that the neurodegeneration is "secondary" to an injury, disease, disorder or condition that causes primary neuronal damage. The claims are not directed to the treatment of the various injuries and diseases listed in claim 4. They are directed to the inhibition of neuronal degeneration that is secondary to the primary neuronal damage caused by any of those various injuries or diseases. Claim 4 is dependent from claim 3. If claim 3 is not objectionable, then claim 4 cannot be objectionable on this score. The same is true of claims 23 and 42. Accordingly, reconsideration and withdrawal of this objection are respectfully urged.

Furthermore, 37 CFR 1.144 specifies that a petition from a restriction requirement can be deferred until after final action on or allowance of claims to the invention

elected. Thus, an applicant is within his or her rights to refrain from amending the claims to limit them to the elected embodiment until after any such petition is filed and decided. Thus, the claims have not been amended at the present time to limit them to stroke only (the elected embodiment). Accordingly, it is requested that this objection be held in abeyance until after final action or allowance on the elected embodiment.

Rejection under 35 U.S.C. 112, first paragraph

In item 5 of the Office Action, the examiner wrote:

> Claims 1-4, 6, 10, 21-23, 25-26, 40-42, and 44-46 are rejected under the 35 U.S.C 112 ¶1, because the specification, while being enabling for the reduction of the size of ischemia-induced neural damage and decreasing the amount of neuronal cell loss within the retina by administration of poly-Glu,Tyr, does not reasonably provide enablement for promoting nerve regeneration, or preventing neuronal degeneration, or for amounts effective to prevent, inhibit, or promote nerve regeneration.

The examiner brings here the eight factors to be considered when determining if the disclosure satisfies the enablement requirement as established *In re Wands* (1988). This rejection is respectfully traversed.

With regard to the nature of the invention, the examiner states that treatment of neurological diseases and

prevention of neuronal degeneration is complex and the specification does not show prevention of neurodegeneration.

The claims have now been amended to delete specific reference to prevention. They only require inhibition. Of course, when administered prior to exposure to the primary insult (as in Example 1, for example), inhibition of neurodegeneration will also result in some amount of prevention. Nevertheless, as the claims do not explicitly mention "prevention," this part of the rejection has been overcome.

The examiner further points out:

> The specification does not provide enablement for promoting or inhibiting nerve regeneration, or the amounts of poly-Glu,Tyr effective for such. The specification discloses a prophetic example for determining the number of new neurons born after ischemic stroke. This is set forth in Example 15, beginning on p.49. No actual experiments are reported.

At the end of Example 15, it is said:

> Results showing induction of proliferation and/or differentiation of adult stem cells in the brain will indicate that poly-Glu,Tyr has a positive effect on adult neurogenesis in the brain after ischemia. [page 50, line 14-16].

The examiner writes that the specification does not disclose what constitutes a “positive effect” and comes to the conclusion that, in the context of the example, “positive effect” seems to be a decrease in the number of neurons born.

With all due respect, we do not understand how the examiner arrives to this definition of "positive effect," particularly taking into consideration that at the end of Example 15, p. 50, it is explicitly written that "induction of proliferation and/or differentiation of adult stem cells in the brain …" is indicative of a positive effect on adult neurogenesis.

The examiner states that there are no examples that show that poly-Glu,Tyr changes the number of neurons in any direction. He continues:

> As the specification teaches that the increase in neurogenesis is a consequence of injury, but the art recognizes that neurogenesis is beneficial and correlated with cognitive function, and since there is no disclosure of whether poly-Glu,Tyr increases or decreases neurogenesis, the skilled artisan would essentially have to determine whether the agent increases or decreases neurogenesis, and then determine the dose effective for this function. Given the contradiction between the art, which teaches neurogenesis is beneficial, and the specification which teaches that it is a consequence of injury, it would take undue experimentation by the artisan to practice the method commensurate in scope with the claims.

The examiner has apparently misunderstood the explanation in the specification regarding neurogenesis in the brain. There is no doubt that neurogenesis is beneficial. What is disclosed in Section VI, pages 48-49, of the specification, is that pathologic events such as ischemic

injury stimulate neurogenesis in regions of the brain known to harbor neural stem cells. However, this spontaneous neurogenesis after injury, albeit beneficial, is not effective because the new neural cells die and do not survive for prolonged periods.

The inventors have performed more experiments and are able to show actual neurogenesis in the brain. Attached hereto is a paper by Ziv et al. entitled "A novel immune-based therapy for stroke induces neuroprotection and supports neurogenesis", recently accepted by *Stroke*, a journal of the American Heart Association. In this paper, two of the inventors of the present application - Michal Schwartz and Eti (Ester) Yoles are the two last authors. Also attached hereto is a Declaration under 37 CFR 1.132 by Michal Schwartz and Ester Yoles attesting to the veracity of the procedures and results reported in the *Stroke* manuscript.

As shown in the *Stroke* paper (and as attested to by the attached Declaration), poly-YE (poly-Glu,Tyr) improved neurological outcome in rats after stroke (Results and Fig. 1), attenuated behavioral deficits after stroke (Results and Fig. 2), and attenuated neuronal loss in the hippocampus (Results and Fig. 3). These results are indicative of neuroprotection. See, for example, Fig. 3, for the dramatic

reduction of neuronal necrosis in the hippocampus following ischemia.

In addition, the *Stroke* paper shows that poly-YE promotes neurogenesis in rats after stroke in brain parts known to undergo spontaneous neurogenesis, e.g., hippocampus (Fig. 4 – increased hippocampal neurogenesis) as well as in brain parts not known to undergo spontaneous neurogenesis, e.g., cortex (Fig. 5 – enhanced stroke-induced cortical neurogenesis).

The inventors wish to explain that, contrary to previous belief, neurogenesis continues throughout most of the adult life of mammals and primates. Progenitor neuronal cells which are present in the sub-ventricular zone and in the dentate gyrus of the hippocampus are responsible for such growth as they proliferate and differentiate into neuronal cells. These cells can also migrate to another part of the brain. As described in the Discussion section of the *Stroke* paper, poly-YE is shown to cause a neurogenesis-promoting effect illustrated by increased number of newly formed neurons in the hippocampus and the appearance of newly formed neurons in the cerebral cortex of treated animals. The fact that an increased number of new neurons with mature phenotype was detected in the hippocampus and cortex almost three weeks

after BrdU injection suggests that the effect of poly-YE on neurogenesis is long lasting rather than transient.

The examiner further states that "the specification is not enabling for treatment of all diseases and conditions associated with neural death" [page 5, 2nd full paragraph]. For example, he mentions that regarding ALS there is only a prophetic example. However, as pointed out in the specification, p. 51, lines 27-28, "… it is established that glutamate-based neurotoxicity is part of ALS, part of a process leading to motor neurons' death.", and page 52, line 3-5: "The results … show that poly-Glu,Tyr is effective in protecting RGCs from glutamate toxicity and indicate that poly-Glu,Tyr may be a candidate for treatment of ALS and other motor neuron diseases". Thus, we believe that there is enablement for treatment of ALS.

Treatment of Huntington's disease is also objected to, as are "any disease or condition which does not share a mechanism with those conditions shown to be amenable to treatment", because the neuronal cell death is not caused by glutamate toxicity. The examiner further states: "Thus given the state of the art, the breadth of the claims, and the lack of sufficient guidance and working examples in the specification, it would take undue experimentation on the part

of a skilled artisan to practice the claimed methods commensurate in scope with the claims."

It should be understood that the treatment with poly-Glu,Tyr is intended to cope with the secondary damage/degeneration that follows the primary injury, regardless of the mechanism causing the primary injury. Thus, poly-Glu,Tyr can be used according to the present invention to ameliorate the neurodegeneration associated with a neurological injury (as defined in claim 40), for reducing neurodegeneration caused by a primary injury (as defined in claim 22), to ameliorate the neurodegeneration caused or exacerbated by glutamate toxicity (as defined in claim 26), or to ameliorate a neurological or neurodegenerative disease, disorder or condition (as defined in claim 53), independently of the primary cause of said neurodegenerative disease, disorder or condition.

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

3.2 Claim Rejections – 35 USC 102

Claim 1 has been rejected under 35 USC §102 as being anticipated by Vidovic, 1985, as evidenced by Bussiere et al., 2001. The examiner states that Claim 1 encompasses prevention of neuronal degeneration by administering poly-Glu,Tyr to an

individual in need thereof. The examiner states that Bussiere provides evidence that this includes all subjects, as all subjects lose neurons in advancing age. The examiner calculated that the dose per bodyweight of poly-Glu,Tyr administered by Vidovic to mice is similar to the dose given to rats in the example described in the specification. The examiner concludes that as the Vidovic reference teaches administration of the same dose of the same compound to subjects in need of prevention and inhibition of neurodegeneration, and in need of promotion of nerve regeneration in both the CNS and PNS, and in need of protection of nerves from glutamate toxicity, it anticipates the claimed invention."

As discussed above, the claims have now been amended so that they no longer read on prevention. No combination of Vidovic with Bussiere teach inhibition of neurodegeneration in an individual in need thereof. Accordingly, reconsideration and withdrawal of this rejection is respectfully urged.

The examiner further says that Vidovic teaches that the random copolymer poly-Glu,Tyr induces strong T cell responses and teaches which mouse strains are particularly strong responders in terms of how well their T-cells respond to the poly-Glu,Tyr injections. He also mentions that Vidovic teaches that the T cells are most likely helper-inducers, the

proliferation of T cells by administration of poly-Glu,Tyr, the amount needed to induce this response and the ways subjects with different genetic backgrounds differ in their proliferative T cell responses.

Most interestingly, the inventors were able to show the neuroprotective effect of poly-Glu,Tyr by using C57Bl/6J strain of mice, which were described by Vidovic as marginally responsive. Thus, the neuroprotective effect is most probably not related to the effect that Vidovic describes in his paper. Moreover, Vidovic does not teach administration of poly-Glu,Tyr for protecting neurons from secondary damage.

In any event, claim 1 has now been amended to delete specific reference to prevention. Furthermore, the neuronal degeneration that is being inhibited is defined as "secondary neuronal degeneration." Thus, it must be secondary to a primary injury. This does not read on the treatment of all aging persons, as is allegedly suggested by Bussiere. Accordingly, particularly as presently amended and in light of the above arguments, none of the present claims are anticipated by Vidovic. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claim Rejections - 35 USC 103

Claims 1-3, 21-22, 40, 41 and 45 have been rejected under 35 USC 103(a) as being unpatentable over Kipnis, 2000 (*PNAS* 97:7446-7451) and Vidovic, 1985.

According to the examiner:

> Kipnis teaches administration of copolymer 1 (Cop 1) inhibits the progression of secondary degeneration after nerve crush injury, which is relevant to claims 1-3, 21-22, and 40-41. Kipnis teaches that Cop-1 is a synthetic copolymer of four amino acids, alanine, lysine, glutamic acid and tyrosine (see p. 7446, first column). This protein is similar to, but not the same as, the poly-Glu,Tyr recited in all pending claims as the prior art protein has both alanine and lysine, which are not in the protein used in the claimed methods; in the instant case the protein used only has two of the four amino acids used in the protein from Kipnis. Kipnis teaches that immunization with copolymer-1 not only protects neurons within the retina against secondary injury, but Kipnis also teaches that the reason it has such protective effects is that it evokes an immune response. As the neurons in the retina are part of the central nervous system, the Kipnis reference is clearly on point to inhibition of neuronal degeneration, and promoting nerve regeneration in the CNS, which are recited in generic claim 1. Kipnis also teaches administration of the copolymer to patients suffering from neurological injuries, recited in generic claims 21 and 40. The nerve crush injury is a form of a neurological disorder or condition, recited in claim 45. The reference teaches that the random copolymer Cop-1 is non-encephalitogenic (see p. 7450, top of second column) when injected, and elicits T-cell responses. Kipnis teaches that this T-cell response is the mechanism by which Cop-1 has its protective effect, and

> suggests that this mechanism will be useful for protecting CNS neurons from chronic and acute injury (see p. 7451, final paragraph)… While Cop-1 was known to cross-react with myelin basic protein (MBP), Kipnis teaches that this feature is not what is crucial to the protective aspect of T cells, as the Cop-1 administrations do not result in EAE, and the T-cells evoked by this drug are regulatory in nature (see p. 7450, last paragraph).

The examiner goes on to state:

> Thus, the reference teaches the artisan of ordinary skill that proliferation of T-cells, by any suitable mechanism, is useful for protecting CNS neurons from damage due to chronic or acute injury. However, Kipnis does not teach administration of poly-Glu,Tyr.

The examiner then concludes that it would have been obvious to one of ordinary skill in the art to modify the method of Kipnis, which is a method of providing neuronal protection by administering a random copolymer which induces T-cell proliferation, to administer poly-Glu,Tyr, which Vidovic teaches is a random copolymer that induces T-cell proliferation, with a reasonable expectation of success. The examiner states that the motivation to do so would be to prevent neuronal damage, which Kipnis teaches is accomplished by administration of Cop-1 that induces T-cell proliferation and that the references provide both the motivation and the reasonable expectation of success, as both references teach

that the copolymers induce T-cell proliferation. This rejection is respectfully traversed.

Contrary to the examiner's assertion, poly-Glu,Tyr does not act through induction of T-cell proliferation. As explained in the specification, p. 21, poly-Glu,Tyr down-regulates the regulatory cells' (Treg cells) suppressive effect on the effector T cells (Teff), and the Teff cells home to the site of lesion in the CNS and activate the resident cells, thus boosting the spontaneous protective activity of T cells at the site of lesion or injury.

Kipnis clearly shows that the neuroprotection by immunization with Cop-1 is conferred by activated T cells specific to Cop 1 and cross-reactive with MBP that accumulate at the site of lesion. Kipnis also shows that the same neuroprotective effect can be obtained by administering T cells reactive to Cop-1 and these cells will accumulate at the site of lesion and reduce secondary degeneration in the CNS.

Thus, both Cop-1 and poly-Glu,Tyr augment protective autoimmunity but through completely different mechanisms. Cop-1 induces T helper cells reactive to Cop-1 that home to the lesion site, cross-react with MBP and become activated at the lesion site, while poly-Glu,Tyr does not elicit T cells reactive to poly-Glu,Tyr, but rather down-regulates the suppressive activity of Treg cells on the autoreactive

effector T cells that home to the lesion site and activate resident cells, thus protecting CNS cells from further degeneration and enhances functional recovery.

Vidovic studied the proliferative T-cell response of inbred mouse strains to poly-Glu,Tyr and found it to fall into two categories: some strains responded only marginally (SI=stimulation index lower than 3), whereas other strains mounted a substantial response (SI=3-30). For this purpose, mice were immunized with poly-Glu,Tyr emulsified in CFA. Table 1, p. 3564, shows the mice that were nonresponders (-) and the mice that were responders (+). Among the nonresponder mice, we find the C57BL/6J mice (second strain in the table). These mice were used in some of the experiments in the present application. They were injected with poly-Glu,Tyr in PBS (without CFA) and found to be protected against glutamate toxicity (Example 2) and against cognitive impairment induced by psychotomimetic agents (see Example 23). In other examples, rats were used.

Accordingly, it would not have been prima facie obvious at the time the present invention was made that poly-Glu,Tyr would be expected to have all the same properties as Cop-1. Indeed, it does not. It works with a completely different mechanism. From the above, it can be seen that claims 1-3, 21-22, 40, 41 and 45 are not obvious in view of

Kipnis and Vidovic. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1-4, 6, 10, 21-23, 25-26, 40-42, 44-46 have been rejected under 35 USC 103(a) as being unpatentable over Kipnis and Vidovic (see above) and further in view of Cecil, *Textbook of Medicine*, 2000, pp. 2092-2109.

The examiner summarizes again that claims 1-3, 21-22, 40, 41 and 45 are obvious over Kipnis and Vidovic because Kipnis teaches that administration of a copolymer which stimulates T cell proliferation is neuroprotective against secondary neural damage and Vidovic teaches that a different random copolymer, poly-Glu,Tyr, also stimulates T-cell proliferation. However, the examiner recognizes that neither Kipnis nor Vidovic teaches administration to patients with ischemic stroke or with conditions caused or exacerbated by glutamate toxicity. The examiner takes the position that Cecil teaches that ischemic stroke, the most common form of stroke, results in neuronal damage and is characterized by secondary neural damage that can be exacerbated by glutamate. The examiner states that on p. 2108, first column, Cecil teaches that neuroprotective drugs currently investigated for protection against the damage induced by ischemic stroke, include those that block the excessive glutamate release typically seen in stroke. Therefore, the examiner considers

that this reference is relevant to claims 4, 6, 10, 23, 25-26, 42 and 44-46, drawn to ischemic stroke and conditions characterized by excessive glutamate. The examiner considers that it would have been obvious "to administer poly-Glu,Tyr for protection in ischemic stroke… as Kipnis is on point to neuroprotection, and Cecil teaches that patients with stroke are in need of such a protection, thereby guiding the artisan to this particular population." This rejection is respectfully traversed.

We believe that our arguments above would be sufficient to answer also to this rejection. Furthermore, none of the references cited by the examiner suggest that either Cop-1 or poly-Glu,Tyr protect from glutamate toxicity. This does not necessarily follow from the damaged optic nerve tests of Kipnis. Thus, there is no reason for anyone of ordinary skill in the art reading these references to believe that poly-Glu,Tyr would provide any amount of neuroprotection to ischemic stroke victims. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Double patenting

Claims 1-4, 6, 10, 21-23, 25-26, 40-42 and 44-46 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of US Patent no. 6,835,711 (the parent patent of this CIP). The

examiner states that, although the conflicting claims are not identical, they are not patentably distinct from each other because in both cases the claims encompass methods of decreasing damage of certain types of neurons, damaged by or subject to damage by glutamate, by administration of poly-Glu,Tyr.

In order to obviate this rejection attached hereto is a terminal disclaimer. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Additional Comments

Attached hereto is an IDS submitting publications of the applications from which the present application claims benefit. The present claims have now been amended to ensure that they are either entitled to the benefit of application 09/893,344, filed June 28, 2001, or application no. 60/527,772, filed December 9, 2003. Note that deletion of specific embodiments from dependent claims does not affect the scope of the entire set of claims as such embodiments are still covered by the generic claims from which they depended. Thus, no estoppel has occurred due to these amendments.

Those claims that are not entitled to the benefit of the former application are entitled to the benefit of the latter. Thus, the earliest publication of the former application on January 2, 2003, is not available as a

reference under 35 USC 102(b) for any claim entitled to the benefit of the latter provisional application. Because the inventive entity of the former application is the same as that of the present application, the former application is also not available as a reference under 35 USC 102(a) or (e). Claims 72 and 58 are unobvious from the disclosure of the publication of the first application, regardless of whether or not they are entitled to any effective filing date earlier than the filing date of the present application.

It is submitted that all the claims now present in this case clearly define over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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